1.    (Amended)   A method for modulating <u>one or more of</u> growth, differentiation [,
or] <u>and</u> survival of a <u>neuronal</u> cell, comprising contacting said cell with an effective amount of a
*hedgehog* polypeptide.

Please add the following new claims:

--49.    A method for modulating one or more of growth, differentiation and survival of a
mammalian neuronal cell responsive to *hedgehog* induction, comprising treating the cell with an
effective amount of a hedgehog polypeptide, thereby altering, relative to the cell in the absence
of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of the
neuronal cell.

50.    A method for modulating one or more of growth, differentiation and survival of a
neuronal cell in an animal, comprising administering to the animal a therapeutically effective
amount of a *hedgehog* polypeptide to alter, relative to the absence of *hedgehog* treatment, at least
one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell-types in said
animal.

51.    A method for inducing neuronal cell growth, comprising contacting a neuronal
cell with a *hedgehog* polypeptide.

52.    A method for inducing a cell to differentiate to a neuronal cell phenotype,
comprising contacting said cell with a *hedgehog* polypeptide.

53.    A method for inducing neuronal cell survival, comprising contacting said cell
with a *hedgehog* polypeptide.

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54.    A method for preventing, treating or reducing the severity of a disorder associated with aging of the nervous system in a subject, comprising administering to a subject a therapeutically effective amount of a *hedgehog* polypeptide to alter, relative to the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell-types in said subject.

55.    The method of claim 54, wherein said disorder is Alzheimer's Disease or Parkinson's Disease.

56.    A method of preventing, treating or reducing the severity of a neurodegenerative disorder, comprising administering to said subject a therapeutically effective amount of a *hedgehog* polypeptide to alter, relative to the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell-types in said subject.

57.    The method of claim 56, wherein said disorder is selected from the group consisting of Parkinson's Disease, Huntington's Disease, Pick's Disease, Ballism, Guillain-Barre Syndrome, Amylotrophic Lateral Sclerosis, spinocerebellar degenerations and chronic peripheral neuropathy.

58.    The method of claim 57, wherein said neuronal cells are cholinergic neurons, GABAnergic neurons or striatal neurons.

59.    A method of preventing, treating or reducing the severity of an acute, subacute or chronic injury to the nervous system in a subject, comprising administering to a subject a therapeutically effective amount of a *hedgehog* polypeptide to alter, relative to the absence of

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*hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell-types in said subject.

60. The method of claim 59, wherein said injury is selected from the group consisting of traumatic injury, chemical injury, vasal injury, vasal deficit, infectious injury, inflammatory injury and tumor-induced injury.

61. The method of claim 60, wherein said inflammatory injury is a result of a chronic inflammatory disease.

62. The method of claim 61, wherein said inflammatory disease is multiple sclerosis.

63. The method of claim 60, wherein said vasal injury is ischemia resulting from a stroke.

64. A method for preventing the degeneration or premature death of neuronal cells in a subject, comprising administering to said subject neuronal cells which have been contacted with an effective amount of a *hedgehog* polypeptide, thereby altering, relative to the cell in the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of said neuronal cell.

65. The method of claim 64, wherein said administered neuronal cells are introduced into a subject by cerebral grafting.

66. The method of claim 65, wherein said administered neuronal cells are derived from fetal or neonatal animals.

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67.     The method of claim 64, wherein said administered neuronal cell is a neuronal stem cell.

68.     The method of claim 67, wherein said neuronal stem cell is a neural crest cell.

69.     The method of claim 50, 54, 56 or 59, wherein said *hedgehog* protein is administered in combination with one or more other neurotrophic factors.

70.     The method of claim 69, wherein said other neurotrophic factor is selected from the group consisting of CNTF, BNTF and NGF.

71.     A method of preventing, treating or reducing the severity of a disorder of the peripheral nervous system in a subject, comprising administering to a subject a therapeutically effective amount of a *hedgehog* polypeptide to alter, relative to the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell-types in said animal.

72.     The method of claim 71, wherein said disorder affects smooth muscle tissue and endocrine tissue, such as glandular tissue.

73.     The method of claim 72, wherein said disorder is tachycardia or atrial cardiac arythmia.

74.     The method of claim 71, wherein said disorder affects sensory or motor neurons.

75. The method of claim 74, wherein said disorder is selected from the group consisting of CNS, trauma, infarction, infection, metabolic disease, nutritional deficiency, toxic agents and chromic pain syndrome.

76. The method of claim 1, wherein said neuronal cell is a neural progenitor cell.

77. The method of claim 1, wherein said neuronal cell differentiates into a cell having a particular neural phenotype, such as a neuron or a glia.

78. The method of claim 1, wherein said neuronal cell is in the central nervous system or the peripheral nervous system.

79. The method of claim 78, wherein said *hedgehog* treatment repairs central or peripheral nerve damage.

80. The method of claim 1, wherein said *hedgehog* polypeptide mimics the effect of a naturally-occurring *hedgehog* protein.

81. The method of claim 1, wherein said *hedgehog* polypeptide antagonizes the effects of a naturally-occurring *hedgehog* protein.

82. The method of claim 1, wherein said *hedgehog* polypeptide comprises an amino acid sequence identical or homologous with all or a portion of an amino acid sequence designated in one of SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:34, SEQ ID NO:40 or SEQ ID NO:41.

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83.     The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid identical or homologous with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

84.     The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 80% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

85.     The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 90% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

86.     The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 95% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

87.     The method of claim 1, wherein said *hedgehog* polypeptide is encoded by a nucleic acid capable of hybridizing with a nucleic acid sequence designated in one of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 or SEQ ID NO:7.

88.     The method of claim 1 wherein said *hedgehog* polypeptide is encoded by a nucleic acid capable of hybridizing under stringent hybridization conditions with a nucleic acid

sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:7.

89.    The method of claim 1, wherein said *hedgehog* polypeptide is a bioactive fragment of a *hedgehog* polypeptide.

90.    The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence encoded by a nucleic acid which hybridizes under stringent conditions to a sequence selected from the group consisting of residues 310-567 of SEQ ID NO:1, residues 304-561 of SEQ ID NO:2, residues 91-348 of SEQ ID NO:3, residues 304-561 of SEQ ID NO:4, and residues 301-558 of SEQ ID NO:5.

91..    The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence encoded by a nucleic acid which hybridizes under stringent conditions to a sequence selected from the group consisting of residues 64-567 of SEQ ID NO:1, residues 64-561 of SEQ ID NO:2, residues 1-348 of SEQ ID NO:3, residues 73-561 of SEQ ID NO:4, and residues 70-558 of SEQ ID NO:5.

92.    The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence encoded by a nucleic acid which hybridizes under stringent conditions to a sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6 and SEQ ID NO:7.

93.    The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 80 percent identical with a sequence selected from the group consisting of

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residues 104-189 of SEQ ID NO:8, residues 102-187 of SEQ ID NO:9, residues 31-116 of SEQ ID NO:10, residues 102-187 of SEQ ID NO:11, and residues 101-186 of SEQ ID NO:12.

94.     The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 70 percent identical with a sequence selected from the group consisting of residues 27-189 of SEQ ID NO:8, residues 22-187 of SEQ ID NO:9, residues 1-116 of SEQ ID NO:10, residues 25-187 of SEQ ID NO:11, and residues 24-186 of SEQ ID NO:12.

95.     The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 60 percent identical with an amino acid sequence selected from the group consisting of residues 27-425 of SEQ ID NO:8, residues 22-396 of SEQ ID NO:9, residues 1-336 of SEQ ID NO:10, residues 25-437 of SEQ ID NO:11, residues 24-418 of SEQ ID NO:12, residues 24-475 of SEQ ID NO:13, residues 1-312 of SEQ ID NO:14, and an extracellular fragment thereof of at least 50 amino acids.

96.     The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence encoded by a naturally occurring vertebrate *hedgehog* gene.

97.     The method of claim 96, wherein said *hedgehog* gene is a mammalian *hedgehog* gene.

98.     The method of claim 97, wherein said *hedgehog* gene is a human *hedgehog* gene.

99.     The method of claim 1, wherein said polypeptide includes a *hedgehog* amino acid sequence which is encoded by at least a portion of a *hedgehog* gene of vertebrate origin

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corresponding to residues 64-567 of SEQ ID NO:1, residues 64-561 of SEQ ID NO:2, residues 1-348 of SEQ ID NO:3, residues 73-561 of SEQ ID NO:4, and residues 70-558 of SEQ ID NO:5.

100. The method of claim 1, wherein said *hedgehog* amino acid sequence is represented in the general formula SEQ ID NO:41.

101. The method of claim 1, wherein said polypeptide has an approximate molecular weight of 19kD.

102. The method of claim 1, wherein said polypeptide includes at least 150 amino acid residues of the N-terminal half of a *hedgehog* protein.

103. The method of claim 1, wherein said polypeptide binds to a *patched* protein.

104. The method of claim 103, wherein said *patched* protein is a *patched* protein of a vertebrate organism

105. The method of claim 1, wherein said *hedgehog* polypeptide comprises an amino acid sequence identical or homologous to an amino acid sequence designated in SEQ ID NO:34.

106. The method of claim 1, wherein said *hedgehog* polypeptide modulates the differentiation of neuronal cells.

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